Hepatitis Panels

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Guidelines

Hepatitis Panels

Viral hepatitis is a serious health problem in many areas of the world, including Asia, Japan, and the United States. Viruses from five viral families have been identified and characterized. These viruses differ in their characteristics, modes of spread, and the consequences of both short- and long-term disease. Because new forms of hepatitis that are not associated with the identified etiologic agents continue to be recognized, the hepatitis viruses are considered to be among the causes of emerging and reemerging infectious diseases. Indeed, the candidate hepatitis viruses under investigation include blood-borne and enterically transmitted agents.

Important research areas in the program are as follows:

1. Characterization and study of hepatitis agents, especially their replication strategies, structural biology, host immunologic and pathological responses, and mechanisms of chronicity. Crucial to progress is development of model systems such as in vitro cultivation, cell lines, and small animal models, as well as clinical research. Hepatitis C is the predominant focus.

2. Development and evaluation of vaccines, antiviral agents, and immunomodulators for prevention and treatment. The Hepatitis Panels emphasize development of (a) vaccines for hepatitis C and more potent vaccines for hepatitis B and (b) therapeutic measures for chronic carriers of hepatitis B virus and hepatitis C viruses. Rational development depends on a strong commitment to basic and applications research. The Panels are working to achieve exchange of preclinical information and to develop common clinical protocols.

3. Seroepidemiologic studies to determine the incidence, prevalence, and clinical importance of the infection and disease. Implicit in these objectives is development of meaningful diagnostic methods to detect the disease agent, antibodies induced by it, and the stages of disease.

4. Investigation of the natural history of hepatitis and related diseases. This research includes long-term studies to determine disease patterns and the importance of chronic hepatitis, cirrhosis, and hepatocellular carcinoma as sequelae of viral hepatitis, fulminant hepatitis, and extrahepatic manifestations of hepatitis virus infections.

Five-Year Summary

Broad Goals

The long-term objective of the Hepatitis Panels' program is to reduce the burden of disease by defining conditions for the control of viral hepatitis by prophylaxis, therapy, and improved environmental conditions.

Progress and Accomplishments

Previous research accomplishments of the Hepatitis Panels include development and implementation of control measures (1) to prevent infection with hepatitis A virus, by use of vaccine containing the inactivated virus, and (2) to prevent infection with hepatitis B virus (HBV), by sensitive diagnostic testing to screen blood and blood products and by administration of effective recombinant hepatitis B vaccines, which are now used in universal immunization programs. During the past 5 years, the joint meetings of the U.S. and Japan Hepatitis Panels have increasingly focused on the need to identify therapeutic agents for patients with chronic hepatitis B and C infections who are at risk for cirrhosis and hepatocellular carcinoma (HCC). These fatal complications of chronic viral hepatitis occur in the United States and Japan and are only partially responsive to therapy. In both countries, the increase in prevalence of disease due to infection with hepatitis C virus (HCV) has been greater than the increase in prevalence of disease due to HBV infection.

Hepatitis C Virus

For almost a decade, treatment with interferon has resulted in a sustainable reduction in liver fibrosis and termination of viral replication in approximately 15%-20% of patients with chronic hepatitis C. Results obtained during the last 3 years indicate that the efficacy of interferon relates to its ability to rapidly reduce or eliminate replication of HCV in the liver, coupled with a slower, probably immune-mediated clearance of residual virus-producing cells. The combination of interferon with ribavirin significantly enhances the proportion of sustained viral responses to about 30%. Response with both therapeutic regimens is greatly diminished in patients infected with genotype 1, the most common HCV genotype in the United States and Japan. A major effort of the joint Hepatitis Panel meetings has been discussion and definition of differences in the approaches to use of these therapeutic agents in the United States and Japan and better understanding of the effect of such differences on therapeutic outcome. These meetings have led to the Panels' wider recognition of the potential value of therapy with high-dose interferon to induce response, which is common in Japan, and adjunctive therapy with ribavirin, which was first evaluated and licensed in the United States.

Despite the partial therapeutic success obtained with interferon and ribavirin, the Panels have recognized the need to identify both different targets and candidate small-molecule inhibitors of viral replication. Accordingly, there has been a strong focus on understanding the organization and structure of the genome of HCV and related viruses. The Panels have reported on efforts to obtain a detailed understanding of key components of viral replication: (1) the internal ribosome entry site, an RNA structure that promotes the translation of the viral polyprotein by a unique mechanism; (2) NS3 serine proteinase, which is responsible for the post-translational processing of the polyprotein; and (3) NS3 RNA helicase and NS5B RNA-dependent RNA polymerase. These research efforts have led to the partial or complete characterization of the atomic-level structures of each of these important components of the viral replication machinery, as well as the development of in vitro or in vivo systems that permit high-throughput screening of candidate molecules. An additional strategy has been the development of infectious molecular clones of HCV, valuable reagents that have made it possible to use reverse molecular genetics to study HCV functions. This focus on the need for better antiviral agents has led to increasing involvement of industry scientists in joint meetings of the Hepatitis Panels and closer collaboration among academic, government, and industry scientists.

Also fundamental to the issue of developing better therapeutic agents for hepatitis C is the need to better understand the clinical course of this infection and the underlying mechanisms that lead to cirrhosis and HCC. Knowledge of these mechanisms is limited both by the inability to propagate the virus efficiently in cultured cells and by the lack of a small animal that permits viral replication and that could serve as a model for HCV infections in humans. Highlighting the current state of ignorance about the mechanisms underlying hepatitis C pathogenesis is the realization that most deaths related to hepatitis C in the United States are due to liver failure and cirrhosis, whereas in Japan, death occurs significantly more often because of complications of liver cancer rather than cirrhosis.

The Hepatitis Panels have actively supported a number of binational studies that address these important issues of pathogenesis. Recent studies include the characterization of transgenic mice with hepatitis C

that are at risk for hepatic steatosis and HCC. These mice have been developed independently in the United States and Japan, and reports on the research have been presented in recent joint meetings of the Panels. Further study of the mice is certain to shed light on important nonimmune mechanisms underlying the liver injury in hepatitis C, and findings may point the way to development of novel therapeutic agents. Such studies follow a long history of contributions made to the understanding of chronic hepatitis B infection and the immune response to it that have stemmed from the development and characterization of transgenic mice with hepatitis B that express various segments of the HBV genome.

Hepatitis B Virus

Over the past 5 years, the Panels' major activities related to HBV have focused on elucidating the immune mechanisms underlying viral clearance, viral persistence, and the development of HCC in persons chronically infected with this virus. Studies in transgenic mice and in experimentally infected chimpanzees have shown that viral replication is inhibited directly by cytokines elaborated by noncytotoxic immune effector cells and that the development of cancer is intricately linked to the presence of inflammation elicited by an active but ineffectual immune response that fails to eradicate the infection.

Treatment options for chronic hepatitis B have expanded with the licensure of lamivudine, a nucleoside analogue that inhibits the reverse transcriptase activity of HBV. The clinical response to this drug and the emergence of viral resistance to it through the selection of YMDD variants of the virus have been important topics of study in the United States and Japan. The clinical significance of these HBV variants has yet to be determined, but with their appearance comes a return in the hepatitis B viremia to levels approaching those present before therapy. The frequent selection of these variants during long-term lamivudine therapy suggests the need for adjunctive therapy with an additional antiviral agent, much as combination therapy is the standard today for treatment of HIV infections. The joint Panel meeting has become a forum where candidate antiviral agents and immune modulators to treat hepatitis B have been presented to informed, critical audiences from both countries.

Members of the Japanese Panel have documented the dramatic decrease in transfusion-transmitted hepatitis C that has accompanied the implementation of sensitive diagnostic methods for screening blood and blood products in Japan. These efforts to make the blood supply safe are being reinforced by the introduction of ultrasensitive nucleic acid tests to detect hepatitis B, hepatitis C, and HIV-1 in the United States and Japan. The test can also detect virus in persons with persistent infection but undetectable levels of serological markers, as in cases of hepatitis B mutants.

Emerging Infections

In recent years, the Panels have solicited from a large number of Pacific Rim nations epidemiologic and clinical data on the continuing emergence of hepatitis virus infections. These studies have been the focus of several recent meetings and have shown unique epidemiologic patterns of emergence of HCV in Japan and Korea. The curves for age-related prevalence that are derived from seroepidemiologic studies show dissemination of the virus in these countries approximately 50 years ago. Hepatitis C is a more recently emerging threat to health in Thailand and other countries, but there is a continuing predominance of hepatitis B in association with liver cancer in all countries of the region except Japan, where most liver cancer is now associated with HCV infection. Hepatitis E virus is endemic in China, India, and other countries of Southwest Asia.

Viral Hepatitis and Hepatocellular Carcinoma

Contrasting models of direct viral oncogenesis versus inflammation-mediated carcinogenesis have been proposed by Japanese investigators. After early steatosis, liver cancer develops in transgenic mice expressing relatively high levels of core protein from HCV. This finding implicates core protein in the development of HCC and suggests that the virus is directly involved in hepatocarcinogenesis without causing inflammation. In another study from Japan, immune-mediated liver cell injury due to HBV or HCV infection appeared to result from cell killing and stimulation of mitosis, producing transformation and chromosomal instability. These contrasting models of direct viral oncogenesis and inflammation-mediated carcinogenesis may not be mutually exclusive, but rather additive or synergistic in the development of HCC in patients with chronic HBV or HCV infection.

Interferon treatment for chronic hepatitis C appears to protect against the development of HCC more frequently when only serum concentrations of alanine aminotransferase (a measure of liver function) normalize, even though HCV RNA has not been eliminated. The compound glycyrrhizin, which is extracted from the roots of *Glycyrrhizia glaba*, has long been used in Japan to normalize these serum concentrations without

direct antiviral effect. A well-controlled, retrospective study of long-term treatment with this compound showed that relative risk of HCC in patients who were not treated with the compound was 2.49, compared with the risk in patients who were treated with the compound.

Hepatitis virus researchers from China, India, Korea, Nepal, Thailand, Vietnam, Singapore, and Taiwan participated in a meeting to commemorate the 20th anniversary of the Hepatitis Panels, which was held in Chiba, Japan, in March 1999. The conference addressed the patterns of mortality and etiology of HCC in Asian countries in relation to the prevalence of chronic infection with hepatitis B and hepatitis C in each country. One study showed that the mortality from HCC in adults has been increasing but that the prevalence of this cancer in children began to decrease with the start of the immunization program for hepatitis B.

The Japanese Cooperative Medical Science Program is now supporting collaborative studies on the relationship between viral hepatitis and HCC in Nepal, where hepatitis E, B, and C and hepatitis of unknown etiology are major health care problems.

Candidate Hepatitis Viruses

A novel flavivirus, GB virus C (otherwise known as hepatitis G virus), was identified and molecularly cloned by U.S. investigators. Although preliminary data suggested that GB virus C was the cause of sporadic transfusion-associated hepatitis, more complete epidemiologic studies indicate that infection with this virus is not associated with liver injury. Nonetheless, although it is not a hepatitis virus, GB virus C causes persistent infection and may be transmitted by blood transfusion. The consequences of long-term infection with this virus remain unknown.

Another group of blood-borne viruses that has been identified during the past 5 years is represented by TT virus, a circular DNA virus first identified by Japanese investigators. Infection with TT virus may be persistent and is highly prevalent in Japanese populations and, to a lesser extent, in U.S. populations. Like GB virus C, TT virus has unknown health consequences and may be commonly transmitted by blood transfusion. No tests have been implemented to screen blood and blood products for the presence of this virus. Although initial epidemiologic studies suggested that TT virus might be the elusive non-A-E hepatitis agent, findings now indicate that it is a common virus with a wide variety of genotypes, infecting humans without resulting in liver disease in most instances.

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